PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
C07D 501/46, A61K 31/545	A1	WO 92/21683
		(43) International Publication Date: 10 December 1992 (10.12.92)

(21) International Application Number: PCT/JP92/00685

(22) International Filing Date: 27 May 1992 (27.05.92)

(30) Priority data:
9111406.6 28 May 1991 (28.05.91) GB

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

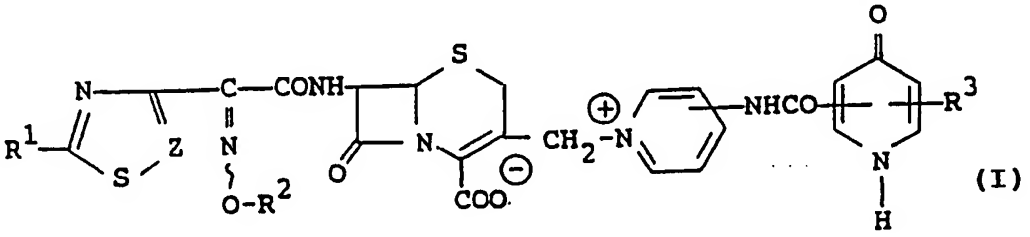
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : SAKANE, Kazuo [JP/JP]; 15, Azayamagata, Mino, Kawanishi-shi, Hyogo 666-01 (JP). YAMANAKA, Hideaki [JP/JP]; 77-10, Kuzuhanakanoshiba 2-chome, Hirakata-shi, Osaka 573 (JP). OGAWA, Yasuhiro [JP/JP]; 2-10, Midorigaoka 2-chome, Ikeda-shi, Osaka 563 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: NEW CEPHEM COMPOUNDS



(I)

(57) Abstract

New cephem compounds of formula (I), wherein R^1 is amino or protected amino, Z is N or CH, R^2 is hydrogen or an organic group, and R^3 is hydroxy or protected hydroxy, and pharmaceutically acceptable salts thereof which are useful as a medicament.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

DESCRIPTION

NEW CEPHEM COMPOUNDS

TECHNICAL FIELD

This invention relates to new cephem compounds and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some cephem compounds have been known as described, for example, in U.S. Patent 4,443,444.

DISCLOSURE OF INVENTION

The present invention relates to new cephem compounds and pharmaceutically acceptable salts thereof. More particularly, it relates to new cephem compounds and pharmaceutically acceptable salts thereof, which have antimicrobial activities, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a method for treating infectious diseases in human being and animals.

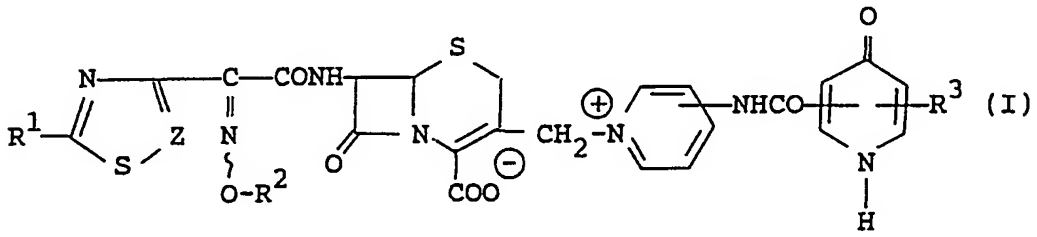
Accordingly, one object of the present invention is to provide the cephem compounds and pharmaceutically acceptable salts thereof, which are highly active against a number of pathogenic microorganisms.

Another object of the present invention is to provide processes for the preparation of the cephem compounds and salts thereof.

A further object of the present invention is to provide pharmaceutical composition comprising, as an active ingredient, said cephem compounds or their pharmaceutically acceptable salts.

Still further object of the present invention is to provide a method for treating infectious diseases caused by pathogenic microorganisms, which comprises administering said cephem compounds to infected human being or animals.

The object cephem compounds of the present invention are novel and can be represented by the following general formula (I) :

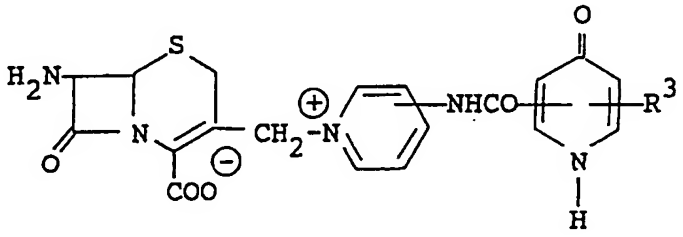


(I)

wherein R^1 is amino or protected amino,
Z is N or CH,
R^2 is hydrogen or an organic group, and
R^3 is hydroxy or protected hydroxy.

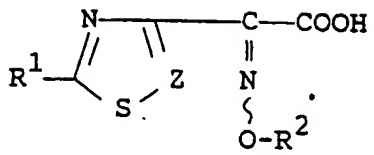
The object compound (I) of the present invention can be prepared by the following processes.

Process (1)



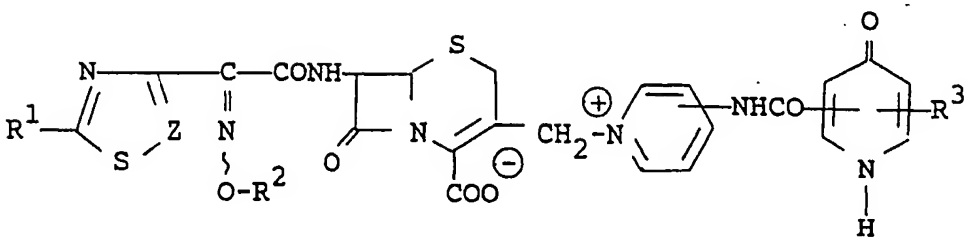
(IIa)

or its reactive derivative at the amino group, or a salt thereof



(III)

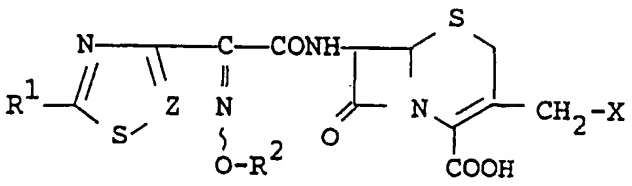
or its reactive derivative at the carboxy group, or a salt thereof



(I)

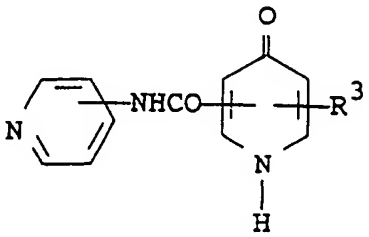
or a salt thereof

Process (2)



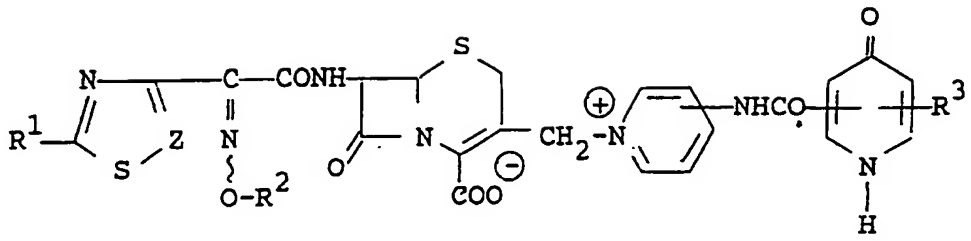
(IV)

or a salt thereof



(V)

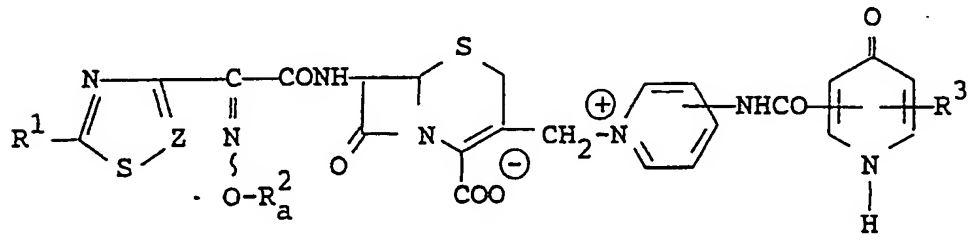
or a salt thereof



(I)

or a salt thereof

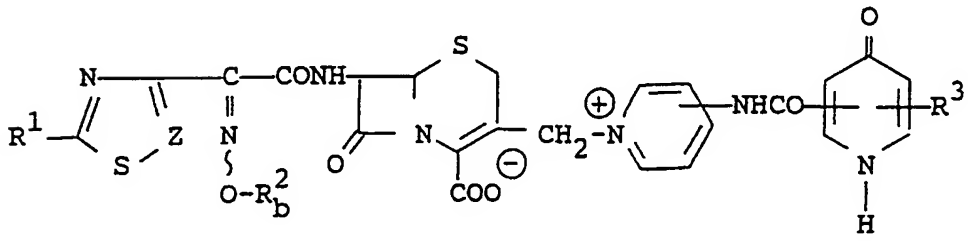
Process (3)



(Ia)

or a salt thereof

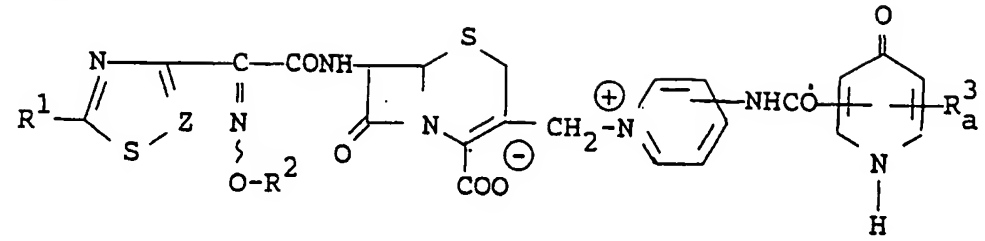
Elimination reaction of the carboxy protective group



(Ib)

or a salt thereof

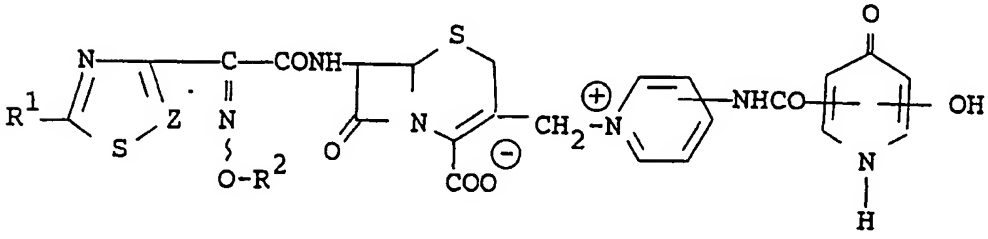
Process (4)



(Ic)

or a salt thereof

↓ Elimination reaction of the hydroxy protective group



(Id)

or a salt thereof

wherein R^1, R^2, R^3 and Z are each as defined above,

R^2_a is protected carboxy(lower)alkyl,

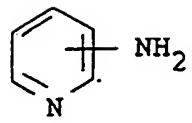
R^2_b is carboxy(lower)alkyl,

R^3_a is protected hydroxy,

X is a leaving group.

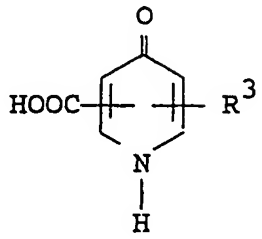
The starting compounds (IIa) and (V) can be prepared by the following Processes.

Process (A)



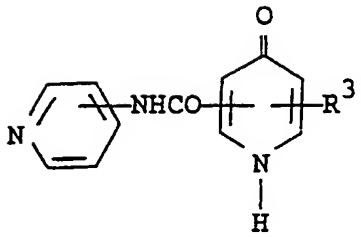
(VI)

or its reactive derivative
at the amino group, or a salt thereof



(VII)

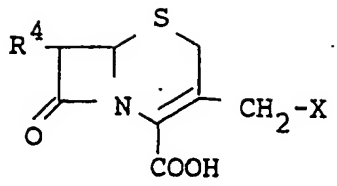
or its reactive derivative
at the carboxy group,
or a salt thereof



(V)

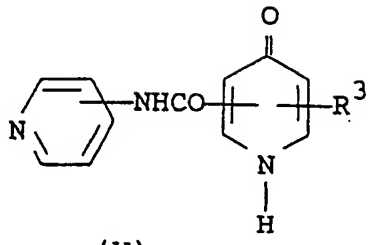
or a salt thereof

Process (B)



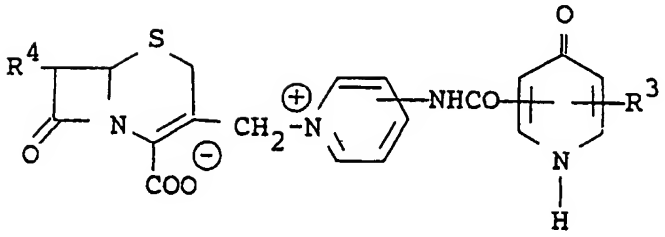
(VIII)

or a salt thereof



(V)

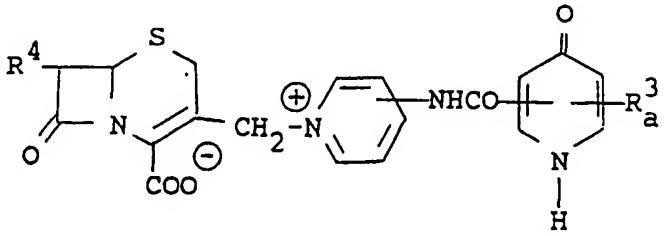
or a salt thereof



(II)

or a salt thereof

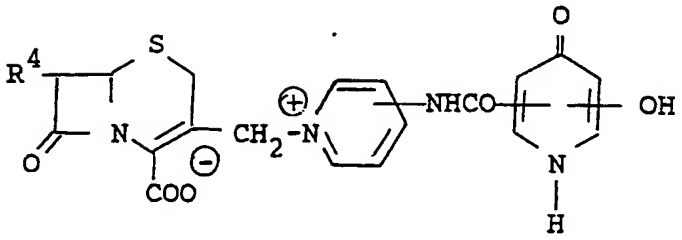
Process (C)



(IIb)

or a salt thereof

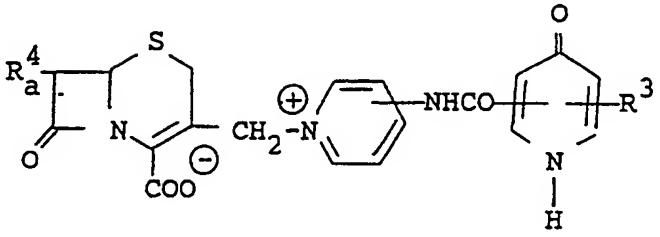
Elimination reaction of the hydroxy protective group



(IIc)

or a salt thereof

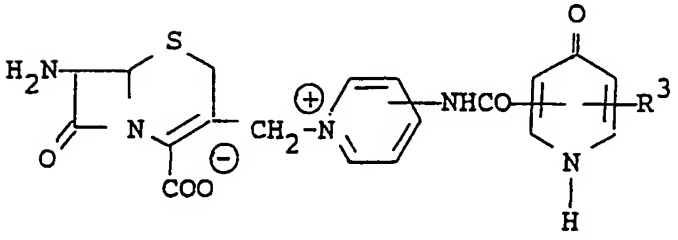
Process (D)



(IId)

or a salt thereof

Elimination reaction of the amino protective group



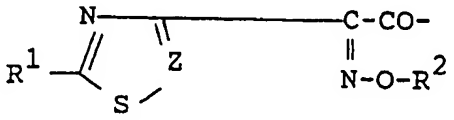
(IIa)

or a salt thereof

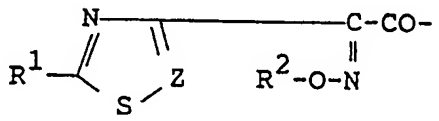
wherein R^3, R^3_a and X are each as defined above,
R^4 is amino or protected amino, and
R^4_a is protected amino.

Regarding the compounds (I), (Ia)~(Id), (III) and (IV), it is to be understood that said compounds include syn isomer, anti isomer and a mixture thereof.

For example, with regard to the object compound (I), syn isomer means one geometrical isomer having the partial structure represented by the following formula :

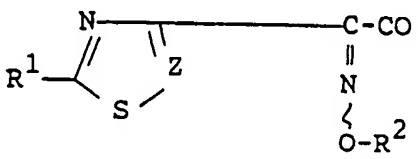


(wherein R^1, R^2 and Z are each as defined above) and anti isomer means the other geometrical isomer having the partial structure represented by the following formula :



(wherein R^1, R^2 and Z are each as defined above), and all of such geometrical isomers and mixture thereof are included within the scope of this invention.

In the present specification and claim, the partial structure of these geometrical isomers and mixture thereof are represented for convenient sake by the following formula :



(wherein R^1, R^2 and Z are each as defined above).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "protected amino" may include an acylamino or an amino group substituted by a conventional protecting group such as ar(lower)alkyl which may have suitable substituent(s) (e.g. benzyl, trityl, etc.) or the like.

Suitable "acyl moiety" in the term "acylamino" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic or heterocyclic ring. And, suitable examples of the said acyl may be lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.); lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tertiarybutoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.); lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.); arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.); aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarbonyl, etc.); ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.); ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like. The acyl moiety as stated above may have suitable substituent(s) such as halogen (e.g. chlorine, bromine, iodine or fluorine) or the like.

Suitable "organic group" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.),

mono(or di or tri)halo(lower)alkyl (e.g. chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, chloroethyl, dichloroethyl, trichloroethyl, fluoroethyl, trifluoroethyl, etc.),

lower alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.),

lower alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3 butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, etc.),

aryl (e.g., phenyl, naphthyl, etc.),

ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.),

carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, protected carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above and protected carboxy moiety can be referred to the ones as exemplified below, and the like.

Suitable "protected carboxy" and "protected carboxy moiety" in the term "protected carboxy(lower)alkyl" may include esterified carboxy and the like. And suitable examples of said ester may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, etc.); lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.); lower alkoxyalkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.); lower alkylthioalkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.);

mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.); lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.); lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester etc.); ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.); aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.); tri(lower)alkyl silyl ester; lower alkylthioester (e.g. methylthioester, ethylthioester, etc.) and the like.

Suitable "protective group" in the "protected hydroxy" may include acyl as mentioned above, phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g. benzyl, 4-methoxybenzyl, etc.), tetrahydropyranyl and the like.

Suitable "leaving group" may be halogen [e.g. chlorine, bromine, iodine, etc.], acyloxy such as sulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, mesyloxy, etc.], lower alkanoyloxy [e.g. acetyloxy, propionyloxy, etc.] or the like.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g.

sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt etc.], an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.], and the like.

Preferred embodiments of the object compound (I) are as follows.

R^1 is amino or protected amino [more preferably acylamino],
Z is N or CH,
R^2 is lower alkyl, carboxy(lower)alkyl or protected carboxy(lower)alkyl [more preferably esterified carboxy(lower)alkyl, most preferably lower alkoxycarbonyl(lower)alkyl], and
R^3 is hydroxy or protected hydroxy [more preferably phenyl(lower)alkyloxy which may have one or more suitable substituent(s)].

The processes for preparing the object and starting compounds of the present invention are explained in detail in the following.

Process (1)

The compound (I) or a salt thereof can be prepared by reacting the compound (IIa) or its reactive derivative at the amino group, or a salt thereof with the compound (III)

or its reactive derivative at the carboxy group, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IIa) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IIa) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IIa) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide [e.g. N-(trimethylsilyl)acetamide], bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (IIa) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (III) may include a conventional one uses in a β-lactam chemistry, an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 1-hydroxy-1H-benzotriazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$]

ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, benzothiazolyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride;

thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process (2)

The compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

The present reaction may be carried out in a solvent such as acetone, chloroform, acetonitrile, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction. The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming. The reaction is usually carried out in the presence of an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, tri(lower)alkylamine [e.g. trimethylamine, triethylamine,

diisopropylethylamine etc.], picoline, alkali metal alkanoate [e.g. sodium 2-ethylhexanoate, etc.], N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

Process (3)

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to elimination reaction of the carboxy protective group. Suitable method of this elimination reaction may include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.],

methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.) copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used

in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process (4)

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to elimination reaction of the hydroxy protective group. This reaction can be carried out in a similar manner to that of the aforementioned Process (3), and therefore the reagents to be used and the reaction conditions (e.g. solvent, reaction temperature, etc.) can be referred to those of the Process (3).

Process (A)

The compound (V) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the amino group, or a salt thereof with the compound (VII) or its reactive derivative at the carboxy group, or a salt thereof.

This reaction can be carried out in a similar manner to that of the aforementioned Process (1), and therefore the reagents to be used and the reaction conditions (e.g. solvent, reaction temperature, etc.) can be referred to those of the Process (1).

Process (B)

The compound (II) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (V) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as alcohol (e.g., methanol, ethanol,

isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction is usually carried out in the presence of an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, tri(lower)alkylamine [e.g. trimethylamine, triethylamine, diisopropylethylamine etc.], picoline, or the like.

Process (C)

The compound (IIc) or a salt thereof can be prepared by subjecting the compound (IIb) or a salt thereof to elimination reaction of the hydroxy protective group. This reaction can be carried out in a similar manner to that of the aforementioned Process (3), and therefore the reagents to be used and the reaction conditions (e.g. solvent, reaction temperature, etc.) can be referred to those of the Process (3).

Process (D)

The compound (IIa) or a salt thereof can be prepared by subjecting the compound (IId) or a salt thereof to elimination reaction of the amino protective group. This reaction can be carried out in a similar manner to that of the aforementioned Process (3), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (3).

Suitable salts of the object and starting compounds and their reactive derivatives in Process (1)~(4) and

(A)~(D) can be referred to the ones as exemplified for the compound (I).

The object compound (I) and pharmaceutically acceptable salts thereof are novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents.

Now in order to show the utility of the object compound (I), the test data on MIC (minimal inhibitory concentration) or representative compound of this invention are shown in the following.

Test method :

In vitro antibacterial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Trypticase-soy broth (10^8 viable cells per ml) was streaked on heart infusion agar (HI-agar)containing graded concentrations of representative test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 37°C for 20 hours.

Test compound :

7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer)

Test result :

MIC (μg/ml)

Test strain	Test compound (1)
P. areruginosa 26	≦ 0.025

For therapeutic administration, the object compound (I) and pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration.

The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

In needed, there may be included in the above preparations, auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg of the object compound (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a suspension of 5-(4-methoxybenzyloxy)-2-carboxy-4(1H)-pyridone (115 g), 3-aminopyridine (39.35 g) and anhydrous 1-hydroxybenzotriazole (62.3 g) in N,N-dimethylformamide (1.15 ℓ) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (88.2 g) at 25°C. After stirred at the same temperature for an hour, the reaction mixture was stirred at 43°C for 4 hours. After cooling to 20°C, the mixture was poured into a mixture of ice-water (4.6 ℓ), diisopropyl ether (1.15 ℓ), ethyl acetate (2.3 ℓ) and sodium chloride (400 g). The mixture was stirred for 30 minutes and the resulting precipitate was collected by filtration. The precipitate was suspended in tetrahydrofuran (4 ℓ), and 1N sodium hydroxide (200 ml) and sodium chloride (100 g) was added. The separated tetrahydrofuran layer was dried over magnesium sulfate (1 kg), and evaporated under reduced pressure to dryness. The resulting residue was triturated with chloroform and dried to give 5-(4-methoxybenzyloxy)-2-(3-pyridylcarbamoyl)-4(1H)-pyridone (105.5 g).

IR (Nujol) : 3320, 1668, 1580 cm^{-1}

NMR (DSMO-d_6, δ) : 3.76 (3H, s), 5.23 (2H, s), 6.96, 7.41 (2H, ABq, J=8.6Hz), 7.42 (1H, m), 7.61 (1H, s), 8.25-8.30 (2H, m), 8.31 (1H, s), 9.03 (1H, s)

Preparation 2

To a solution of 5-(4-methoxybenzyloxy)-2-(3-pyridylcarbamoyl)-4(1H)-pyridone (63.65 g) and diisopropylethylamine (31.5 ml) in N,N-dimethylformamide (640 ml) was added 7β-formamido-3-chloromethyl-3-cephem-4-carboxylic acid (50 g) at -5°C. After stirred at 5°C for 2 hours, the reaction mixture was poured into ethyl acetate (6.4 ℓ). The resulting precipitate was collected by filtration,

washed with ethyl acetate and dried under reduced pressure to give crude 7β-formamido-3-[3-[{5-(4-methylbenzyloxy)-4-oxo-1,4-dihydropyridin-2-yl}carbonylamino]-1-pyridinio]-methyl-3-cephem-4-carboxylate (84 g). The resultant compound (84 g) was added to the ice-cooled mixture of dichloromethane (160 ml), anisole (80 ml) and trifluoroacetic acid (320 ml) by portions. The reaction mixture was stirred under ice-cooling for 2 hours. The resulting solution was poured into diisopropyl ether (2.8 ℓ). The precipitate was collected by filtration, washed with diisopropyl ether and ethyl acetate, and dried under reduced pressure to give 7β-formamido-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]-methyl-3-cephem-4-carboxylate trifluoroacetate (70 g). To a suspension of the resultant compound (69.5 g) in methanol (695 ml) was added conc. hydrochloric acid (44.7 ml) under ice-cooling. The solution was stirred at 22°C for 4 hours. The resulting solution was poured into a mixture of acetone (1.85 ℓ) and ethyl acetate (1.85 ℓ). The precipitate was collected by filtration, washed with ethyl acetate and dried under reduced pressure to give crude objective compound (56 g). The crude compound (56 g) was dissolved into water (560 ml). The aqueous solution was adjusted to pH 1.0 with 6N hydrochloric acid, subjected to column chromatography on Diaion HP-20 (Trademark : Mitsubishi Kasei Corporation) (560 ml), and eluted with water. The fractions containing the objective compound was collected. To the collected aqueous solution (925 ml) was added isopropylalcohol (2.3 ℓ) by portions under ice-cooling. The resulting precipitate was collected by filtration, washed with isopropyl alcohol and dried under reduced pressure over phosphorus pentoxide to give 7β-amino-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate dihydrochloride (19.2 g).

NMR (D_2O, δ) : 3.39, 3.76 (2H, ABq, J=17.9Hz), 5.23 (1H, d, J=4Hz), 5.35 (1H, d, J=4Hz), 5.41, 5.66 (2H, ABq, J=14Hz), 7.42 (1H, s), 7.91 (1H, s), 8.09 (1H, dd, J=6Hz and 9Hz), 8.64 (1H, d, J=9Hz), 8.77 (1H, d, J=6Hz), 9.64 (1H, s)

Example 1

To a suspension of 7β-amino-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate dihydrochloride (15.46 g) in tetrahydrofuran (309 ml), N-(trimethylsilyl)acetamide (78.75 g) was added and the mixture was warmed to 38°C. To the resulting solution of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetic methanesulfonic anhydride (syn isomer) (10.57 g) was added at 7°C. After stirred at 3~5°C for 40 minutes, the reaction mixture was poured into a mixture of ethyl acetate (2.5 ℓ) and acetic acid (37.78 ml). The mixture was stirred at room temperature for 1.5 hours, and the resulting powder was collected by filtration, washed with ethyl acetate (300 ml) and dried in vacuo. The powder (27.9 g) was dissolved in water (279 ml) by adjustment to pH 8 with 1N sodium hydroxide, and the solution was adjusted to pH 6.5 with 1N hydrochloric acid, and the resulting precipitate was removed by filtration, and the filtrate was subjected to column chromatography on Diaion HP-20 (140 ml) and eluted with water. The eluate (1290 ml) was adjusted to pH 1 with 6N hydrochloric acid, and the resulting precipitate was removed by filtration, and the filtrate was subjected to column chromatography on Diaion HP-20 (420 ml). The column was washed with water (4.2 ℓ). The desired product was eluted with 30% aqueous tetrahydrofuran, and the eluate (1.26 ℓ) was evaporated to 850 ml and cooled to 7°C. The resulting powder was

collected by filtration and dried in vacuo to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer) (9.82 g).

IR (Nujol) : 1770 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.46 (3H, s), 1.47 (3H, s), 3.24 and 3.68 (2H, ABq, J=17.8Hz), 5.31 and 5.63 (2H, ABq, J=14.4Hz), 5.31 (1H, d, J=4.8Hz), 5.90 (1H, d, J=4.8Hz), 7.20 (1H, s), 7.71 (1H, s), 7.96 (1H, dd, J=5.7Hz and 8.3Hz), 8.52 (1H, d, J=8.3Hz), 8.66 (1H, d, J=5.7Hz), 9.53 (1H, s)

Example 2

To a suspension of 7β-amino-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate dihydrochloride (670 mg) in tetrahydrofuran (13 ml), N-(trimethylsilyl)acetamide (3.41 g) was added and the mixture was warmed to 40°C. To the resulting solution, 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetyl chloride hydrochloride (syn isomer) (334 mg) was added at 7°C. After stirred at 20°C for 30 minutes, the reaction mixture was poured into a mixture of ethyl acetate (104 ml) and acetic acid (1.64 ml). The mixture was stirred at room temperature for one hour, and the resulting powder was collected by filtration, washed with ethyl acetate (26 ml) and dried in vacuo. The powder (1.12 g) was dissolved in water (25 ml) by adjustment to pH 9 with 1N sodium hydroxide solution, and the solution was adjusted to pH 1 with 6N hydrochloric acid, and the resulting precipitate was removed by filtration, and the filtrate was subjected to column chromatography on Diaion HP-20 (25 ml). The column was washed with water (200 ml). The desired product was eluted with 35% aqueous methanol, and the eluate (112 ml) was evaporated to 18 ml and cooled

to 5°C. The resulting powder was collected by filtration and dried in vacuo to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer) (180 mg).

IR (Nujol) : 1760 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 3.19 and 3.68 (2H, ABq, J=17.8Hz), 3.92 (3H, s), 5.25 and 5.63 (2H, ABq, J=14.8Hz), 5.29 (1H, d, J=4.8Hz), 5.87 (1H, d, J=4.8Hz), 7.10 (1H, s), 7.59 (1H, s), 7.89 (1H, dd, J=5.8Hz and 9.5Hz), 8.43 (1H, d, J=9.5Hz), 8.61 (1H, d, J=5.8Hz), 9.48 (1H, s)

Example 3

To a solution of 5-(4-methoxybenzyloxy)-2-(3-pyridylcarbamoyl)-4(1H)-pyridone (441 mg) and sodium 2-ethylhexanoate (1.25 g) in N,N-dimethylformamide (8 ml), 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-chloromethyl-3-cephem-4-carboxylic acid trifluoroacetate (2.33 g) was added at 5°C. After stirred at 5°C for 4 hours, the reaction mixture was added dropwise into ethyl acetate (80 ml). The resulting powder was collected by filtration and dried in vacuo. The powder (2.28 g) was dissolved in a mixture of water (30 ml) and acetone (120 ml), and the solution was subjected to column chromatography on silica gel (45.5 g). The desired product was eluted with 80% aqueous acetone, and the eluate was lyophilized to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-[{5-(4-methoxybenzyloxy)-4-oxo-1,4-dihydropyridin-2-yl}-carbonylamino]-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer). To a solution of the compound (250 mg) in formic acid (2.5 ml), 35% hydrochloric acid (0.177 ml) was

added at room temperature. After stirred at room temperature for 1.5 hours, the solution was added dropwise into a mixture of ethyl acetate (20 ml) and acetone (10 ml). The resulting powder was collected by filtration and dried in vacuo. The powder was dissolved in water (13 ml) by adjustment to pH 8 with 1N sodium hydroxide solution, and the solution was adjusted to pH 1 with 6N hydrochloric acid, and the resulting precipitate was removed by filtration, and the filtrate was subjected to column chromatography on Diaion HP-20 (6.5 ml). The column was washed with water (32.5 ml). The desired product was eluted with 35% aqueous methanol, and the eluate was lyophilized to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer) (79 mg).

IR (Nujol) : 1770 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.46 (3H, s), 1.47 (3H, s), 3.24 and 3.68 (2H, ABq, J=17.8Hz), 5.31 and 5.63 (2H, ABq, J=14.4Hz), 5.31 (1H, d, J=4.8Hz), 5.90 (1H, d, J=4.8Hz), 7.20 (1H, s), 7.71 (1H, s), 7.96 (1H, dd, J=5.7Hz and 8.3Hz), 8.52 (1H, d, J=8.3Hz), 8.66 (1H, d, J=5.7Hz), 9.53 (1H, s)

Example 4

To a suspension of 7β-amino-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate dihydrochloride (780 mg) in tetrahydrofuran (15.6 ml), N-(trimethylsilyl)acetamide (3.98 g) was added and the mixture was warmed to 38°C. To the resulting solution, S-2-benzothiazolyl 2-(2-aminothiazol-4-yl)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino)ethanethioate (syn isomer) (867 mg) was added at 7°C. After stirred at room temperature for one hour,

the reaction mixture was poured into a mixture of ethyl acetate (125 ml) and acetic acid (1.9 ml). The mixture was stirred at room temperature for 30 minutes. The resulting powder was collected by filtration, washed with ethyl acetate (30 ml), water (22 ml) and acetone (6 ml) and dried in vacuo to give 7β-[2-(2-aminothiazol-4-yl)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)-carbonylamino}-1-pyridino]methyl-3-cephem-4-carboxylate (syn isomer). To a suspension of the compound (504 mg) in anisole (2 ml), trifluoroacetic acid (2.5 ml) was added dropwise at 7°C. After stirred at room temperature for 2 hours, the resulting solution was poured into isopropyl ether (50 ml). The resulting powder was collected by filtration and dried in vacuo. The powder was dissolved in water (15 ml) by adjustment to pH 7 with 1N sodium hydroxide, and the solution was adjusted to pH 1 with 6N hydrochloric acid, and the resulting precipitate was removed by filtration, and the filtrate was subjected to column chromatography on Diaion HP-20 (15 ml). The column was washed with water (75 ml). The desired product was eluted with 50% aqueous isopropyl alcohol, and the eluate (120 ml) was evaporated to 50 ml and cooled to 5°C. The resulting powder was collected by filtration and dried in vacuo to give 7β-[2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer) (89 mg).

IR (Nujol) : 1770 cm^{-1}

NMR (D_2O-$NaHCO_3$, δ) : 1.46 (6H, s), 3.24 and 3.64 (2H, ABq, J=17.7Hz), 5.29 (1H, d, J=4.8Hz), 5.30-5.54 (2H, m), 5.87 (1H, d, J=4.8Hz), 6.96 (1H, s), 7.18 (1H, s), 7.55 (1H, s), 7.90-8.00 (1H, m), 8.40-8.60 (2H, m), 9.25 (1H, s)

Example 5

(1) To a solution of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer) (900 mg) in 4N-sulfuric acid (3 ml) was added ethanol (6 ml) at 5°C with stirring and the mixture was stirred for 0.5 hour at 5°C. To a solution was added dropwise ethanol (14 ml) under stirring at 5°C. Then the resulting precipitates were collected by filtration and dried to give 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate sulfate (syn isomer) (480 mg).

IR (Nujol) : 1770, 1670 (sh) cm^{-1}

NMR (DMSO-d_6, δ) : 1.43 (6H, s), 3.44 and 3.59 (2H, ABq, J=18Hz), 5.22 (1H, d, J=5Hz), 5.58 and 5.70 (2H, ABq, J=14Hz), 7.78 (1H, s), 8.08-8.18 (2H + 1H, m), 8.21 (1H, s), 8.85 (1H, d, J=6Hz), 8.98 (1H, d, J=8Hz), 9.71 (1H, s)

The following compound was obtained according to a similar manner to that of Example 5-(1).

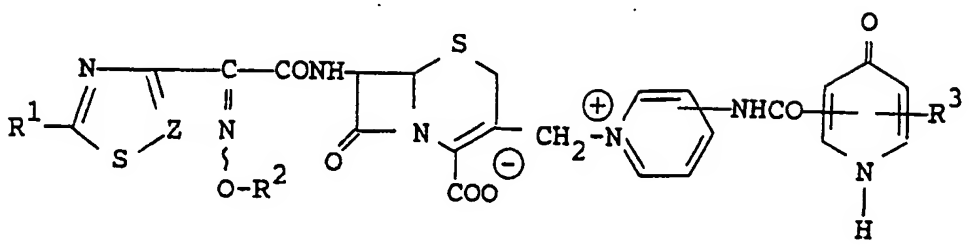
(2) 7β-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate hydrochloride (syn isomer).

IR (Nujol) : 1770, 1670 cm^{-1}

NMR (DMSO-d_6, δ) : 1.43 (6H, s), 3.30-3.63 (2H, m), 5.20 (1H, d, J=5Hz), 5.55 and 5.60 (2H, ABq, J=14Hz), 5.95 (1H, dd, J=5Hz, 8Hz), 7.63 (1H, s), 8.13 (1H, s), 8.10-8.20 (3H, m), 8.78 (1H, d, J=6Hz), 8.95 (1H, d, J=9Hz), 9.56 (1H, d, J=8Hz), 9.69 (1H, br s)

CLAIMS

1. A compound of the formula :



wherein R^1 is amino or protected amino,
Z is N or CH,
R^2 is hydrogen or an organic group, and
R^3 is hydroxy or protected hydroxy,
or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein
R^1 is amino or acylamino,
R^2 is hydrogen, lower alkyl, carboxy(lower)alkyl or protected carboxy(lower)alkyl, and
R^3 is hydroxy or phenyl(lower)alkyloxy which may have one or more suitable substituent(s).

3. A compound of claim 2, wherein
R^2 is hydrogen, lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl, and
R^3 is hydroxy or lower alkoxyphenyl(lower)alkyloxy.

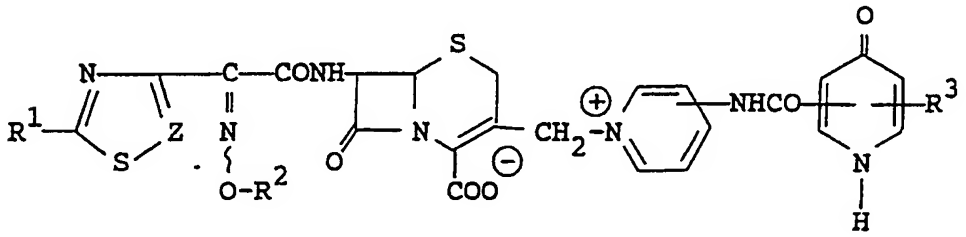
4. A compound of claim 3, wherein
R^2 is hydrogen, lower alkyl, carboxy(lower)alkyl or lower alkoxycarbonyl(lower)alkyl.

5. A compound of claim 4, wherein
R^1 is amino,
Z is N,

R^2 is carboxy(lower)alkyl, and
R^3 is hydroxy.

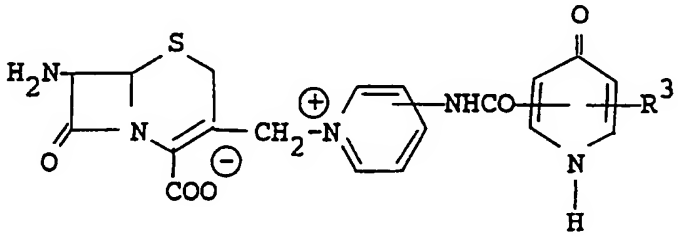
6. A compound of claim 5, which is 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-[3-{(5-hydroxy-4-oxo-1,4-dihydropyridin-2-yl)carbonylamino}-1-pyridinio]methyl-3-cephem-4-carboxylate (syn isomer) or a pharmaceutically acceptable salts thereof.

7. A process for preparing a compound of the formula :

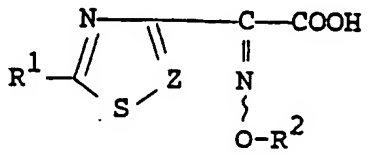


wherein R^1 is amino or protected amino,
Z is N or CH,
R^2 is hydrogen or an organic group, and
R^3 is hydroxy or protected hydroxy,
or a salt thereof,
which comprises

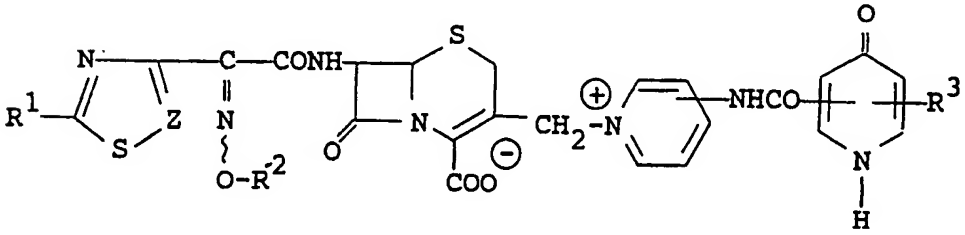
(1) reacting a compound of the formula :



wherein R^3 is as defined above,
or its reactive derivative at the amino group, or a salt thereof with a compound of the formula :

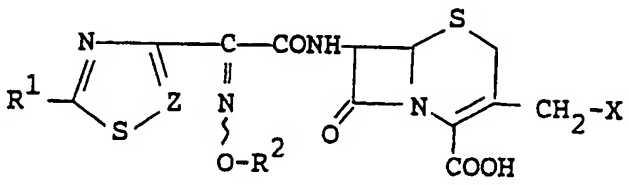


wherein R^1, R^2 and Z are each as defined above,
or its reactive derivative at the carboxy group,
or a salt thereof to give a compound of the formula :

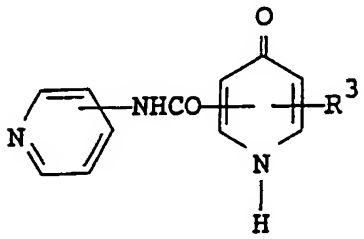


wherein R^1, R^2, R^3 and Z are each as defined above,
or a salt thereof, or

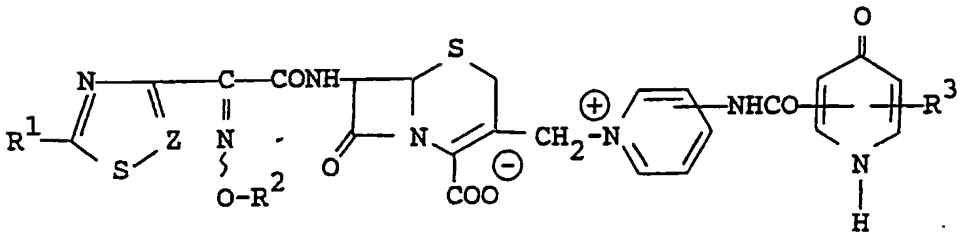
(2) reacting a compound of the formula :



wherein R^1, R^2 and Z are each as defined above, and
X is a leaving group,
or a salt thereof with a compound of the formula :

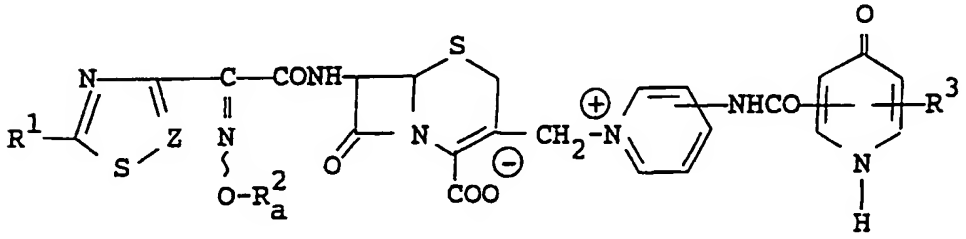


wherein R^3 is as defined above,
or a salt thereof to give a compound of the formula :

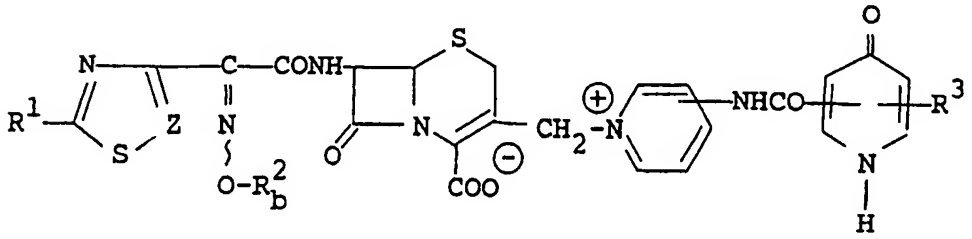


wherein R^1, R^2, R^3 and Z are each as defined above,
or a salt thereof, or

(3) subjecting a compound of the formula :

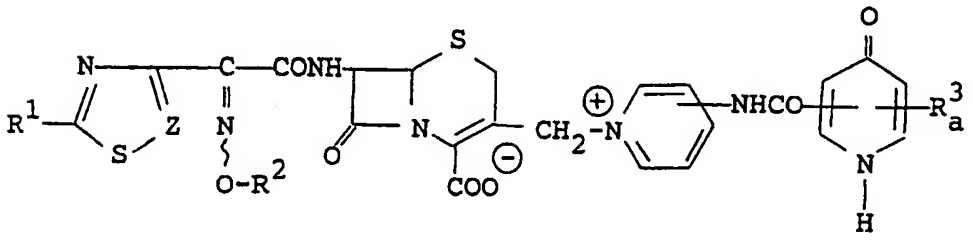


wherein R^1, R^3 and Z are each as defined above, and R^2_a is protected carboxy(lower)alkyl, or a salt thereof to elimination reaction of the carboxy protective group to give a compound of the formula :

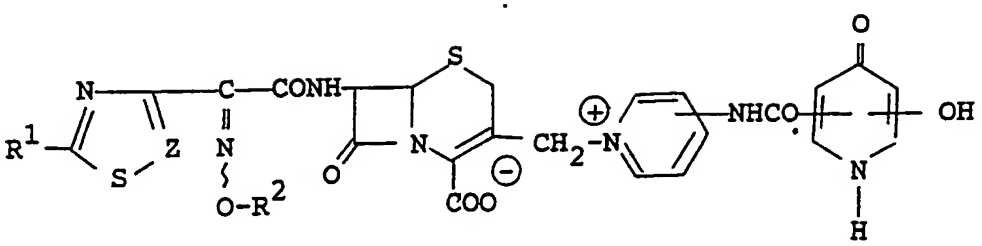


wherein R^1, R^3 and Z are each as defined above, and R^2_b is carboxy(lower)alkyl, or a salt thereof, or

(4) subjecting a compound of the formula :

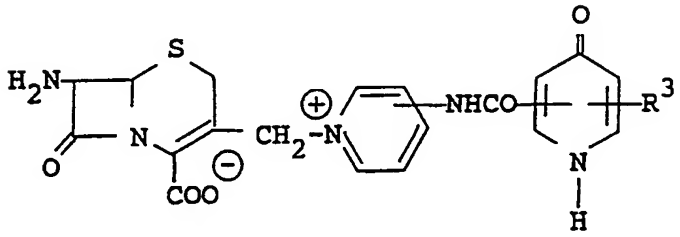


wherein R^1, R^2 and Z are each as defined above, and R^3_a is protected hydroxy, or a salt thereof to elimination reaction of the hydroxy protective group to give a compound of the formula :



wherein R^1, R^2 and Z are each as defined above, or a salt thereof.

8. A compound of the formula :



wherein R^3 is hydroxy or protected hydroxy, or a salt thereof.

9. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

10. A method for the treatment of infectious diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

11. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an antimicrobial agent.

INTERNATIONAL SEARCH REPORT

International Applicat lo PCT/JP 92/00685

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 501/46 A 61 K 31/545

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 501/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0345671 (FUJISAWA) 13 December 1989, see pages 1,2; pages 40-47, claims	1-11

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12-08-1992	17. 08. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mariella Wallberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIO. L SEARCH REPORT

PCT/JP 92/00685

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human body the search has been carried out and based on the alleged effects of the compound.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9200685 SA 59657

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 27/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0345671	13-12-89	AU-B- 622906	30-04-92
		AU-A- 3583989	07-12-89
		JP-A- 2028187	30-01-90